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RAUWOLFIA VOMITORIA Afz.

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AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

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EDITORIAL

UNIFORM STATE LEGISLATION

CURRENT efforts to encourage state legislative bodies to adopt food and drug laws which are consistent with existing federal legislation, as well as that in other states, is highly commendable and a rational approach. The difficulties encountered by drug manufacturers in their distributive system when they must take into consideration the vagaries and inconsistencies met in going from state to state can be unbelievably complex. A great deal of time must be spent by the legal departments of certain drug manufacturers in order to make sure that the conditions of sale, labelling, and distribution do not cause the company to run afoul some special provision in a few states or even in ordinances adopted by a certain municipality.

By and large, the Food, Drug and Cosmetic Act and the regulations issued by the Food and Drug Administration through the Department of Health, Education and Welfare are reasonable and give full measure of protection to the public insofar as the sale and distribution of drugs are concerned. The Durham-Humphrey Amendment we cannot endorse for reasons which we have pointedly expressed on these editorial pages. Briefly, this Amendment has endeavored to spell out in precise terms what may and may not be done legally by the pharmacist in spite of the fact that these matters properly belong among his professional prerogatives. It has also given added impetus to the distribution and sale of drugs for use by the laity based on self-diagnosis and home treatment. This, we believe is not in the interest of public welfare, although it may be of considerable benefit commercially to the manufacturers of proprietary remedies.

The purpose of this editorial is not, however, to discuss the Durham-Humphrey Amendment but to point out a matter which is being overlooked in many states where uniform drug legislation is being adopted with the blessing of all parties, including organized pharmacy. While, in principle, uniform drug legislation is highly desirable, there is a certain responsibility resting on each of the health professions, state departments of health, and, most of all, on the legislative bodies themselves. This responsibility is to make certain that actions taken by the federal government, legislative or otherwise, are completely sound when subjected to critical evaluation. It is in-

cumbent upon all of us not to make the fatal mistake of assuming that, because a thing is judged correct by the federal government and its agencies, that this alone makes it right without question. Such an attitude of mind is one that might soon cause the complete neutralization of all state laws as effective means of giving the citizens of a state the protection which they have a right to expect from their duly elected state representatives. State legislators are surely not elected by their constituents for the purpose of giving rubber stamp approval to every action taken by the federal government, thus making it binding on intrastate affairs as it is on interstate affairs. Citizens of every state have a right to expect a critical appraisal and evaluation of each matter based strictly on its merits.

The reason for this present editorial will be seen in the recent action of the Food and Drug Administration permitting the over-the-counter sale in any retail outlet of certain mixtures of phenobarbital and ephedrine. This was done solely on the basis that such combinations are lacking in hypnotic action. This has been followed by efforts to introduce a model uniform state law which would permit the same practice within the states where present laws prohibit such sale.

It is not the editor's purpose to enter into a long discourse giving his personal opinion judging this action by the Food and Drug Administration as unsound. This has already been done in the state in which he is located. Rather it is the purpose to call to the attention of all those concerned with state legislation the need to recognize their reponsibility and not accept "lock, stock, and barrel" decisions such as this unchallenged. It is even more important to have state laws so written that what is done by the federal government does not automatically become the law or the regulation within the state. It is of the utmost importance in our system of government in this country that proper checks and balances be maintained. The only way that a humble citizen such as this writer can voice his opinion in a way that it will have some little effect is to do it on a state level. If this last avenue of approach is to be surrendered meekly by the device of accepting federal regulations without question, then simple citizens, such as the undersigned, will be lost and their cries of no avail. One need not be a Democrat to subscribe to the principle of States' rights. Indeed, certain of these rights are the *sine qua non* of our democracy.

L. F. Tice

THE EFFECT OF SOME ANIONIC AND NON-IONIC SURFACTANTS ON THE ANTIBACTERIAL ACTIVITY OF TOPICAL ANTIBIOTICS *

By Martin Barr ** and Linwood F. Tice ***

Introduction

A MODIFIED formula for Hydrophilic Ointment, U. S. P. XIV (1) was recently suggested (2). It since has been accepted as the official formula for Hydrophilic Ointment, U. S. P. XV (3). The new formula differs from the one it replaces in that polyoxyl 40 stearate[1], a non-ionic surfactant, is used in place of the anionic surfactant, sodium lauryl sulfate.

It has been demonstrated that non-ionic surfactants interfere with the bactericidal activity of certain phenolic antiseptics (4-6). However, there have been relatively few reports on the effect of non-ionics on the antibacterial activity of antibiotics. Bliss and Warth (7) have demonstrated that poloxyethylene 20 sorbitan monooleate [2] brought about a fourfold increase in the activity of polymixin D and B, and circulin against *Escherichia* coli, but had little effect on the activity of chlortetracycline, chloramphenicol, streptomycin, and penicillin against this same organism. Plaxco and Husa (8) reported that the activity of bacitracin in ointments was slowly destroyed in the presence of several non-ionics, including polyoxyethylene 20 sorbitan monooleate.

Since Hydrophilic Ointment, U. S. P. XV contains a non-ionic surfactant and may find use as a vehicle for antibiotic ointments, it is important that there be no interference with antibiotic activity by the surfactant. It was, therefore, decided to study whether there was any such interference produced by polyoxyl 40 stearate. Another non-ionic surfactant, polyoxyethylene 20 sorbitan monostearate [3] and the anionic, sodium lauryl sulfate, the surfactant in Hydrophilic Ointment, U. S. P. XIV, were also studied for their effect on antibiotics.

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* Work supported by a grant from the Atlas Powder Company.

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[1] Myrj 52 ®, Atlas Powder Company.

[2] Tween 80 ®, Atlas Powder Company.

[3] Tween 60 ®, Atlas Powder Company.

The experimental work was divided into two phases. First, the effect of the surfactant on the minimum effective concentration of antibiotics on certain test organisms was observed. Second, the influence of the surfactants on the zones of inhibition produced by ointments containing the antibiotics was determined.

Experimental

Minimum Effective Antibiotic Concentration Method—Using a modified Kolmer Broth Dilution Method (9), the minimum effective concentration of five antibiotics on specific test organisms was determined. The Kolmer Method is a serial dilution method originally devised for the determination of penicillin concentrations in biological specimens. It was found satisfactory for the determination of the minimum effective concentration of the antibiotics under study. The antibiotics[4] studied and the test organisms used with each were: bacitracin (*Micrococcus pyogenes var. aureus*), oxytetracycline hydrochloride (*Sarcina lutea*), neomycin sulfate (*Escherichia coli*), and polymixin B sulfate (*Escherichia coli*). All of these antibiotics are widely used in topical therapy and a pharmacist may be called upon to incorporate them in Hydrophilic Ointment, U. S. P. XV in filling a dermatological prescription. It was originally intended to include tyrothricin in this study but it was not possible to do so because of the limited water solubility of this antibiotic.

In order to determine the effect of the surfactants on the minimum effective concentrations of the antibiotics, media were prepared containing the beef-heart infusion glucose broth used in the Kolmer Method and the antibiotics being studied. The antibiotics were added to the media in such a way that the finished media contained the previously determined minimum effective antibiotic concentration, as well as 0.1, 2, 5, 10, and 100 times the minimum effective concentration. A concentration of 1% w/v of each of the surfactants was also added to some of the media. The finished media were transferred to test tubes as described by the Kolmer Method, inoculated with the test organisms, and the tubes incubated at 37°C. for a period up to thirty days—during which time observations for growth were made. Controls containing the media with the same antibiotic concentrations, but without the surfactants, were included in the experiments. All determinations were carried out in duplicate and repeated twice. The results are given in Table I.

[4] We wish to thank Wyeth Laboratories for providing us with the microbiologically assayed antibiotics used in this work.

TABLE I

THE EFFECT OF 1% w/v POLYOXYL 40 STEARATE, POLYOXYETHYLENE 20 SORBITAN MONOSTEARATE, AND SODIUM LAURYL SULFATE ON THE ANTIBACTERIAL ACTIVITY OF ANTIBIOTICS

Concentration Of Antibiotic per ml.	Polyoxyl 40 Stearate					Polyoxyethylene 20 Sorbitan Monostearate					Sodium Lauryl Sulfate					Control (no surfactant)				
DAYS	1	3	7	14	30	1	3	7	14	30	1	3	7	14	30	1	3	7	14	30
BACITRACIN—*M. pyogenes var. aureus*																				
0.00 units	+	+	+	+	+	+	+	+	+	+	—	—	—	—	—	+	+	+	+	+
0.50 units	+	+	+	+	+	+	+	+	+	+	—	—	—	—	—	+	+	+	+	+
* 5.00 units	—	+	+	+	+	—	+	+	+	+	—	—	—	—	—	—	+	+	+	+
10.00 units	—	—	—	—	+	—	—	—	—	+	—	—	—	—	—	—	—	—	—	+
20.00 units	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
50.00 units	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
OXYTETRACYCLINE HYDROCHLORIDE—*S. lutea*																				
0.00 mcg.	+	+	+	+	+	+	+	+	+	+	—	—	—	—	—	+	+	+	+	+
0.31 mcg.	+	+	+	+	+	+	+	+	+	+	—	—	—	—	—	+	+	+	+	+
* 3.10 mcg.	—	+	+	+	+	—	+	+	+	+	—	—	—	—	—	—	+	+	+	+
6.20 mcg.	—	—	—	+	+	—	—	—	+	+	—	—	—	—	—	—	—	—	+	+
12.40 mcg.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
31.00 mcg.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
310.00 mcg.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

NEOMYCIN SULFATE—*E. coli*

0.00 mcg.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
0.10 mcg.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
* 1.00 mcg.	—	+	+	+	+	—	+	+	+	+	—	—	—	—	—	—	+	+	+	+
2.00 mcg.	—	—	—	+	+	—	—	—	+	+	—	—	—	—	—	—	—	—	+	+
4.00 mcg.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
10.00 mcg.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
100.00 mcg.	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

POLYMIXIN B SULFATE—*E. coli*

0.00 units	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
0.63 units	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
* 6.30 units	—	+	+	+	+	—	+	+	+	+	—	—	—	—	—	—	+	+	+	+
12.60 units	—	—	—	—	+	—	—	—	—	+	—	—	—	—	—	—	—	—	—	+
25.20 units	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
63.00 units	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
630.00 units	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

* = Minimum effective concentration.

— = No growth observed.

\+ = Growth observed.

Cup-Plate Testing of Antibiotic Ointments—Ointments were prepared containing bacitracin, neomycin sulfate, tyrothricin, oxytetracycline hydrochloride, and polymixin B sulfate. Five different ointment bases, differing only in surfactant, were used as the vehicle. They were:

Base 1. Hydrophilic Ointment, U. S. P. XV, containing 5% w/w polyoxyethylene 40 monostearate (polyoxyl 40 stearate, U. S. P.) as surfactant.

Base 2. Hydrophilic Ointment, similar to that of U. S. P. XV, but containing 5% w/w polyoxyethylene 20 sorbitan monostearate as surfactant.

Base 3. Hydrophilic Ointment, U. S. P. XIV, containing 1% w/w sodium lauryl sulfate as surfactant.

Base 4. Base 1 (above) to which was added 1% w/w sodium lauryl sulfate.

Base 5. Base 2 (above) to which was added 1% w/w sodium lauryl sulfate.

Bases 4 and 5 were included in this study to serve as a control for the sodium lauryl sulfate used in Base 3. By this means, it was possible to determine whether the antibiotic or the sodium lauryl sulfate was responsible for the antibacterial action of the ointments containing it.

Fifteen gram quantities of each test ointment were prepared using the bases listed above. The ointments were prepared using the usual precautions for the preparation of sterile ointments. The finished concentration of each of the antibiotic ointments were:

Neomycin Sulfate Ointments—5 mg./Gm.
Bacitracin Ointments—500 units/Gm.
Polymixin B Sulfate Ointments—20,000 units/Gm.
Oxytetracycline Hydrochloride Ointments—30 mg./Gm.
Tyrothricin Ointments—0.5 mg./Gm.

The antibacterial properties of the ointments and bases were determined using the F. D. A. Cup-Plate Method for the testing of antiseptic ointments (10). The test organisms for the ointments and bases were: *Micrococcus pyogenes var. aureus* for the bacitracin

and tyrothricin ointments, *Escherichia coli* for the neomycin sulfate and polymixin B sulfate ointments, and *Sarcina lutea* for the oxytetracycline hydrochloride ointments. The ointments and bases were tested by the Cup-Plate Method two hours after their preparation and also after a five day storage period in the refrigerator. All plates were incubated at 37°C. for 48 hours and then the zones of inhibition produced by the individual ointments and bases, recorded. These results appear in Table II. All results listed in the table represent the average of three determinations for each ointment and base.

TABLE II

THE EFFECT OF SURFACTANTS ON ZONES OF INHIBITION PRODUCED BY ANTIBIOTIC OINTMENTS USING HYDROPHILIC OINTMENTS AS BASES

	Zones of Inhibition Using Different Ointment Bases (in mm.)									
	Base 1		Base 2		Base 3		Base 4		Base 5	
	2 hrs.	5 days	2 hrs.	5 days	2 hrs.	5 days	2 hrs.	5 days	2 hrs.	5 days
Bacitracin [a] 500 units/Gm.	12	10	12	10	12	9	12	10	12	10
Oxytetracycline Hydrochloride [c] 30 mg./Gm.	3	3	3	3	4	4	4	4	4	4
Neomycin Sulfate [b] 5 mg./Gm.	5	5	5	5	5	5	5	5	5	5
Tyrothricin [a] 0.5 mg./Gm.	6	6	5	5	5	5	5	5	5	4
Polymixin B Sulfate [b] 20,000 units/Gm.	4	4	4	4	1	1	4	4	4	4
Base Control [a]	1	1	1	1	2	2	2	2	2	2
Base Control [b]	0	0	0	0	1	1	1	1	1	1
Base Control [c]	0	0	0	0	4	4	4	4	4	4

[a] *M. pyogenes var. aureus* was test organism.

[b] *E. coli* was test organism.

[c] *S. lutea* was test organism.

Base 1—Polyoxyl 40 Stearate (5% w/w).

Base 2—Polyoxyethylene 20 Sorbitan Monostearate (5% w/w).

Base 3—Sodium Lauryl Sulfate (1% w/w).

Base 4—Polyoxyl 40 Stearate (5% w/w) and Sodium Lauryl Sulfate (1% w/w).

Base 5—Polyoxyethylene 20 Sorbitan Monostearate (5% w/w) and Sodium Lauryl Sulfate (1% w/w).

Discussion

Examination of Table I reveals that no interference of antibiotic activity by the surfactants studied was demonstrated. There was bacterial growth observed in some of the solutions containing the non-ionics where the antibiotic concentrations were at the minimum effective levels and slightly above. However, growth was only present where the solutions had been stored in the incubator for at least three days. The fact that growth also occurred in the control solutions of similar antibiotic concentrations where no surfactant was present indicates that the growth was probably due to a reduction in actual antibiotic concentrations resulting from deterioration of the antibiotics. Even a small amount of deterioration would result in a lowering of the antibiotic concentration below the minimum critical level.

It is quite apparent from the results in Table I that sodium lauryl sulfate is an effective antibacterial agent in itself. No growth occurred in solutions containing sodium lauryl sulfate which were inoculated with *Micrococcus pyogenes var. aureus* and *Sarcina lutea*, even when antibiotics were not present. The 1% w/v concentration of sodium lauryl sulfate was not effective against *Escherichia coli* in the test solutions. It is interesting to note that flocculent precipitation occurred upon preparing the neomycin-sodium lauryl sulfate solutions but all precipitates quickly went back into solution. This precipitation did not appear to be deleterious to the antibacterial activity of neomycin in the tests performed.

The results of the antibacterial testing of the ointments recorded in Table II revealed no substantial differences in the activities of the ointments containing bacitracin and tyrothricin, regardless of the surfactants present in the ointment bases. The slightly smaller zones of inhibition produced by these ointments five days after preparation, as compared to those produced by freshly prepared ointments, are rather uniform and are probably due to decomposition of some of the antibiotic in the oil-in-water type emulsion bases.

Neomycin sulfate, in the concentration employed in the ointment tests (5 mg./Gm.), was found to be incompatible with Base 3 where sodium lauryl sulfate is the emulsifier. This is due to the incompatibility between the cationic neomycin and the anionic surfactant, as already reported by Hill, Bester, and Miller (11). This incom-

patibility was not observed with Bases 4 and 5 where both a non-ionic agent and sodium lauryl sulfate were present in the formula. In the antibacterial testing of the neomycin ointment prepared with Base 3, it was found that a zone of inhibition comparable to those obtained with the other neomycin ointments was obtained. While the neomycin-sodium lauryl sulfate reaction does not reduce the activity of the antibiotic, as shown by the agar plate method, the ointment containing this mixture is not pharmaceutically acceptable because of its change in texture due to the incompatibility. Livingood and Mullins (12) have reported that ointments containing sodium lauryl sulfate and neomycin were ineffective clinically. The agar plate test, therefore, may not be a reliable index of the efficiency of such an ointment.

There was a slight incompatibility also observed when the oxytetracycline hydrochloride ointments were prepared using Base 3. This is also probably due to the cationic-anionic incompatibility previously described for the neomycin-sodium lauryl sulfate reaction. The phenomenon observed in these ointments, where the concentration of oxytetracycline hydrochloride is 30 mg./Gm., is not of such an extent as to completely change the texture of the ointment to make it unstable, but it becomes so as the concentration of the antibiotic is increased. The antibacterial activity of the oxytetracycline hydrochloride-Base 3 ointment was similar to those of the antibiotic prepared with the other bases.

No incompatibility was observed with the polymixin B sulfate ointments, but it was observed that the ointments prepared with Base 3 containing sodium lauryl sulfate gave a smaller zone of inhibition than when they were prepared with the other bases.

It is of interest to note that Bases 1 and 2 produced a very small zone of inhibition when *Micrococcus pyogenes var. aureus* was used as the test organism. It is probable that the antibacterial substance in these cases is the propylene glycol contained in the formula as a humectant. The bases containing sodium lauryl sulfate produced zones of inhibition with all the test organisms, as might be expected. These zones were greatest with *Sarcina lutea*.

Thus, it has been demonstrated by the use of two different methods that there is no interference with the antibacterial activity of six commonly used antibiotics by the non-ionic surfactants, polyoxyl 40 stearate and polyoxyethylene 20 sorbitan monostearate, and the

anionic, sodium lauryl sulfate. The authors believe that the cup-plate tests employed, although they are commonly used for the measurement of the antibacterial properties of ointments, are not as sensitive as the minimum effective concentration method utilized in the test for antibiotic interference. This latter method, as previously stated, indicated clearly that there is no interference with the antibacterial activity of the antibiotics by the surfactants employed in this study.

It may, therefore, be stated that Hydrophilic Ointment, U. S. P. XV, containing polyoxyl 40 stearate as surfactant, does not interfere with the antibacterial activity of the antibiotics studied, all of which may find use in dermatologic therapy. This ointment base, in addition to its other advantages (1), has been shown to be compatible with cationic antibiotics which are incompatible with Hydrophilic Ointment, U. S. P. XIV. The possibility of deterioration of certain of the antibiotics in any aqueous vehicle during a long period of storage should not, however, be overlooked.

Summary

1. Using a minimum effective antibiotic concentration method, it has been demonstrated that 1% w/v concentrations of polyoxyl 40 stearate, polyoxyethylene 20 sorbitan monostearate, and sodium lauryl sulfate do not interfere with the antibacterial activity of four antibiotics commonly used topically: bacitracin, oxytetracycline hydrochloride, neomycin sulfate, and polymixin B sulfate.

2. Cup-plate testing for the antibacterial activity of ointments containing the above-mentioned antibiotics and tyrothricin, prepared using hydrophilic ointments of similar formulation except for the surfactants, revealed no differences in the activities of the ointments regardless of the surfactant employed, except for the polymixin B sulfate ointments prepared with Hydrophilic Ointment, U. S. P. XIV which showed a reduced antibacterial activity.

3. Incompatibilities between the cationic antibiotics neomycin and oxytetracycline hydrochloride and Hydrophilic Ointment, U. S. P. XIV have been described. These incompatibilities do not exist with Hydrophilic Ointment, U. S. P. XV.

4. Hydrophilic Ointment, U. S. P. XV has been shown to be a satisfactory vehicle for the five antibiotics included in this study.

Acknowledgment

We wish to thank Dr. Louis Gershenfeld and Dr. Bernard Witlin of the Department of Bacteriology, Philadelphia College of Pharmacy and Science for their suggestions during this study.

REFERENCES

(1) "The United States Pharmacopeia", 14th. rev., Mack Publishing Co., Easton, Pa., 1950, p. 391.

(2) Barr, M., Grim, W. M., and Tice, L. F.: *J. A. Ph. A., 15,* 758-760 (1954).

(3) "The United States Pharmacopeia", 15th. rev., Mack Publishing Co., Easton, Pa., 1955, p. 469.

(4) Bouchardy, M. and Mirimanoff, A., *Pharm. Acta. Helv., 26,* 69-76 (1951).

(5) Bolle, A. and Mirimanoff, A., *ibid.,* 284-290 (1951).

(6) Hadgraft, J. W.: *J. Pharm. & Pharmacol., 6,* 816-829 (1954).

(7) Bliss, E. A. and Warth, P. T., *Ann. N. Y. Acad. Sci., 53,* 38-41 (1950).

(8) Plaxco, J. M. and Husa, W. J., Presented at the A. Ph. A. Convention, May 4, 1955, Miami Beach, Fla.

(9) Kolmer, J. A., Spalding, E. H., and Robinson, H. W., "Approved Laboratory Technic", 5th. Ed., Appleton-Century-Crafts Inc., New York, 1951, pp. 573-574.

(10) Ruehle, G. L. A. and Brewer, C. M., "United States Food and Drug Administration Methods for Testing Antiseptics and Disinfectants", U. S. Dept. Agr. Circ. No. 198 (1931).

(11) Hill, W. T., Bester, J. F., and Miller, O. H.: *Drug Standards, 23,* 80-86 (1955).

(12) Livingood, C. S. and Mullins, J. F., *Postgrad. Med., 12,* 15 (1952).

OBSERVATIONS ON RAUWOLFIA VOMITORIA AFZELIUS *

By Magdalena Cantoria [1] and Heber W. Youngken, Sr.[2]

FOR more than a year the dried roots of *Rauwolfia vomitoria* Afz. (1) have entered the United States from the Belgian Congo, Nigeria, and other West African countries for use by manufacturing pharmacists as a source of reserpine and other alkaloids. Since a number of other species of *Rauwolfia* occur in the areas of Africa where this root is collected, we became interested in the plant and especially in the structure of its root and determined to investigate them in order to provide adequate means for their identification.

Our studies have led into an extensive report which has been presented as a thesis by the first author. This paper represents a partial report of the results of our findings, being limited largely to the plant and its root.

Historical

Rauwolfia vomitoria Afz. (1), was first described in 1818 by Adam Afzelius in his "New Species of Medicinal Plants in Guinea". The bark, root, leaf, and latex of this shrub or tree are reported as having been used by the natives of tropical Africa for various maladies. The leaves are stated to be emetic and, in the proper amount, to be employed for severe cough associated with inflammation of the throat (1). An extract of the bark has been used to destroy vermin (2). Other uses of the drug among the African natives are for fever, indigestion, scabies, diarrhea, colic, and as a tonic and cathartic.

No evidence of its rational pharmacologic action was reported until 1939 when Raymond-Hamet noted that the extract of *Rauwolfia vomitoria* reversed the hypertension produced by adrenalin and abolished its inhibitory effect on respiration (3). He found it to possess a sympathicolytic action.

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* Presented to The Plant Science Seminar, Gainesville, Florida meeting, Aug. 16, 1955.

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[2] Research Professor of Pharmacognosy and Botany, Massachusetts College of Pharmacy.

In 1943, Paris found the root bark of *R. vomitoria* from French Guinea to contain the alkaloids ajmaline, isoajmaline, small quantities of ajmalicine, and traces of a yellow base, probably serpentinine (4). In 1952, alstonine was isolated from the entire roots by Schlittler and his co-workers (5). In 1954, Poisson and co-workers discovered the presence of reserpine in the roots of *R. vomitoria* from French Occidental Africa (6). The same year Goutarel, LeHir, Poisson and Janot isolated two additional alkaloids from this root which they named raumitorine ($C_{22}H_{26}O_4N_2$) and seredine ($C_{23}H_{30}O_5N_2$), representing methoxy derivatives of yohimbine (7).

FIGURE 1. *Rauwolfia vomitoria* Afz. with flowers in terminal umbels of finely pubescent cymes × 1/6.

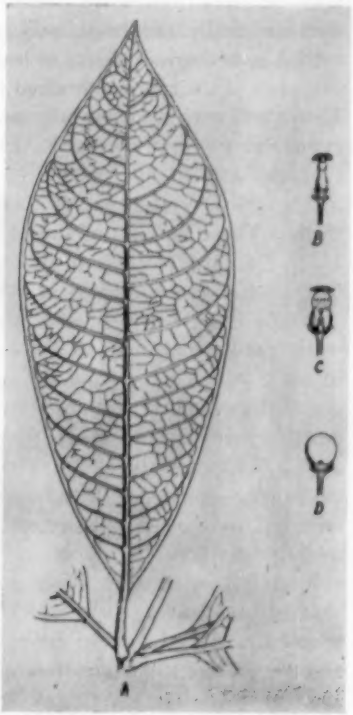


FIGURE 2. *Rauwolfia vomitoria* Afz. A, lower surface of a leaf; B, flower; C, floral parts; D, fruit × 0.87.

The structure of the roots was very briefly and inadequately described by Paris in 1943 (4) owing to the relatively small amount and diameter of the material upon which he worked.

It became apparent from the information on the root histology supplied by his report that a further study of root material on a more extensive scale was necessary in order to positively identify the drug of commerce.

Materials and Methods

The roots used in this investigation consisted of numerous samples of lots of *Rauwolfia vomitoria* roots imported into this country from the Belgian Congo and Nigeria and represented root segments of a very wide range of thicknesses. These were compared macroscopically and microscopically with botanically authenticated roots of *R. vomitoria* attached to herbarium sheets of leaf and flowering and leaf and fruiting branches of the species obtained from the East African Herbarium in Kenya and with a purportedly authentic sample of root segments of *R. vomitoria* supplied by the F. and D. Administration. The description of the plant by Afzelius (1) agreed with the herbarium sheets and enabled verification of the roots and aerial parts attached to them. Three herbarium sheets of *R. vomitoria* borrowed from the U. S. National Herbarium in the Smithsonian Institution, Washington, D. C. were also used in this study.

The dried roots of varying diameters were macerated in boiling water until sufficiently soft to be sectioned on a sliding microtome and in some instances by hand. Transverse, radial-longitudinal and tangential-longitudinal sections of root segments of many different diameters were cut. Some of them were studied separately in water and in phloroglucinol-HCl mounts. Other sections were cleared of starch, stained with safranin and fast green, dehydrated and mounted in Canada balsam, and later studied. Pieces of the bark and of the wood of the roots of different thicknesses were separately subjected to Schulze's Maceration Process (8), the residue then washed and teased apart and the lignified elements studied microscopically. Dried roots of different diameters were mixed and ground and the powder studied microscopically in water and in phloroglucinol-HCl mounts. The starch grains were studied in 70 water mounts of the powder ground from authenticated roots of *R. vomitoria* and in numerous scrapings from such roots. They were also examined in water mounts under polarized light.

Description of Plant

Rauwolfia vomitoria Afz. (Fig. 1) is a shrub or small tree attaining a height of 12 meters and native to tropical Africa. The entire plant is glabrous except the inflorescences. Its leaves, borne on quadrangular branches, are petiolate and borne in whorls of 3 to 5 (Fig. 2A). The leaf blades vary in outline from lanceolate to elliptic to obovate and are more or less acuminate at both ends. They are 2.5 to 21 cm. in length, 10 to 75 mm. in width, membranous and show pinnate-reticulate venation with 7 to 21 pairs of secondary nerves. The petiole is 2 to 25 mm. long and slightly grooved in the middle of its upper side. The flowers (Fig. 2 B, C) occur in terminal umbels of finely pubescent cymes with peduncles 1.8 to 7 cm. long. The pedicels are slender, from less than 1 mm. to 3 mm.

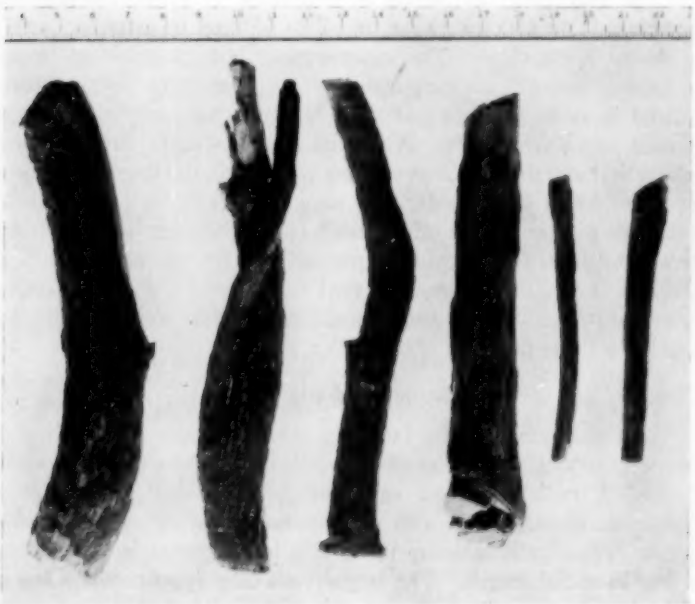


FIGURE 3. Roots of *Rauwolfia vomitoria* Afz. collected between Katera and Kiyebe, Masaka District, Uganda, 4/10/1953. East African Herbarium specimen No. RLX 1106.

long. The calyx consists of 5 nearly free, ovate, obtuse or acute sepals, each about 1 mm. long. The corolla is white, cylindrical, 4 to 8 mm. long with the tube constricted at the mouth, its 5 lobes, ovate, obtuse, 1 to 2 mm. long and overlapping to the left when viewed from the outside. The stamens are 5 and consist of versatile, 2-lobed anthers at the tips of very short filaments attached to the upper part of the corolla tube. The inner wall of the corolla tube beneath the anthers is hairy. The stigma is subspherical and is borne on a slightly thickened style. The two carpels are free and are enclosed at the base by a cup-shaped structure which extends up to ½ to ⅔ the height of the carpels. The fruit is a small subglobose drupe, 2.5 to 5 mm. in diameter, present singly or in pairs and red on maturity (Fig. 2D).

Description of the Root

The root (Fig. 3) occurs in cylindrical or cylindrical-tapering segments, 11 to 150 mm. long, and 2 to 67 mm. in diameter, rarely in obliquely cut chips. The outer surface is light yellowish-brown to brown with a slight purplish hue, irregularly longitudinally striated in younger roots and irregularly longitudinally wrinkled to fissured in mature roots. When handled, the outer surface has a velvety feel and the bark leaves a fine powder on the fingers. Rootlet bases are found in the older root segments. The bark is generally entire but may be peeled off in small areas. The surface sometimes shows oblique notches obviously produced in the cutting of the root. The fracture is fibrous and uneven; the fractured surface exhibits a narrow brownish bark and a broad pale yellow wood. The odor is indistinct and the taste is bitter.

Histology of the Root

In transverse sections (see Fig. 4), *Rauwolfia vomitoria* root shows up to about 75 layers of cork cells in 2 to 14 alternating zones of smaller, radially shorter cells and larger, radially longer cells. The bands of small cells with non-lignified walls consist of up to 4 layers. These cells measure up to 59μ in tangential length and up to 26μ in radial length. The larger cork cells form zones of up to 15 layers of cells. They possess thin, lignified and suberized walls, and measure up to 72μ in tangential length and up to 80μ in radial length. In surface section, the cork cells are polygonal in outline and

in transverse section, they are rectangular. The phellogen consists of 1 or 2 layers of thin-walled rectangular cells.

The cortex in a mature root 33 mm. in diameter is about 130 to 400μ in thickness and is composed of tangentially elongated parenchyma cells, many containing starch grains, and some, monoclinic prisms of calcium oxalate. A few latex cells occur singly in this region. Stone cells, single, or in groups of 2 to about 66, are also found here.

The phloem consists of starch- and crystal-bearing parenchyma cells, sclerenchyma elements, sieve tubes, and companion cells. It is traversed by curving phloem rays. In the middle part of this region in older, thick parts of the root, the stone cells form a continuous band up to about 344μ wide, interrupted only by the phloem rays. This sclerenchyma band consists of thick-walled isodiametric or elongated, branched or unbranched stone cells. The isodiametric

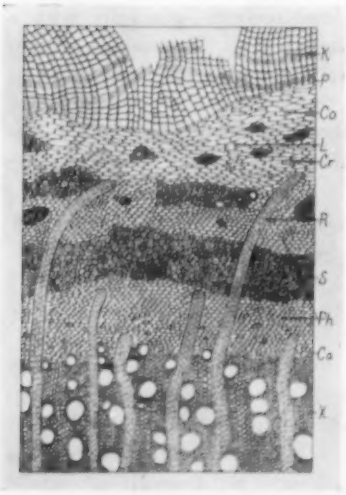


FIGURE 4. Transverse section of the root of *Rauwolfia vomitoria* Afz. K, cork; P, phellogen; Co, cortex; L, latex tube; Cr, prismatic crystal of calcium oxalate; R, vascular ray; S, sclerenchyma; Ph, phloem; Ca, cambium; X, xylem × 32.

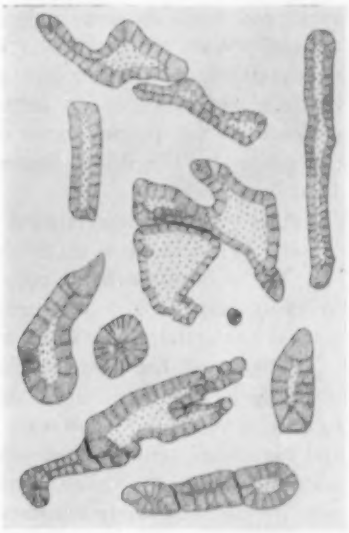


FIGURE 5. Stone cells found in the bark of the root of *Rauwolfia vomitoria* Afz. × 165.

cells are intimately associated with the elongated and branching, wavy-walled cells so that compact aggregates of up to about 300 cells result. The isodiametric cells measure up to 83μ in diameter and the elongated ones are up to 440μ in length. The walls are 5 to 26μ thick and the lumen is generally narrow and often even completely occluded. In the elongated stone cells it is irregular; and in cells with relatively thinner walls the lumen may be quite broad. The pits are simple, and the pore canals are very distinct (See Figs. 5, 6).

The wood occupies about ⅕ to ⅞ of the diameter of the root and is separated from the bark by a wavy cambium consisting of thin-walled cells. The wood includes secondary xylem made up of numerous wood wedges separated by xylem rays, and primary xylem forming a central core. The wedges consist of vessels, tracheids, wood parenchyma cells, wood fibers, and shorter wood rays. All of these possess lignified walls. The vessels are arranged in interrupted radial rows, singly, occasionally in groups of 2 or 3 within the wood wedges. The vessel elements are cylindrical, with oblique or transverse end walls as seen in longitudinal sections, generally with a tail-like process at either end (See Figs. 7, 8). They possess transverse, elliptic pits which are generally simple, very rarely semi-bordered or bordered. In sections, the walls appear beaded. The perforations are simple, round or elliptic, generally terminal, sometimes lateral. The vessel elements are up to 908μ in length and up 173μ in diameter.

The tracheids have tapered ends and are pitted similarly to the vessels. They measure up to about 342μ in length.

The wood parenchyma cells are polysonal, with rounded corners in cross section, and rectangular in longitudinal section. They possess moderately thick walls with bordered pits.

The wood fibers are arranged in radial rows. They are up to 2400μ in length and up to 38μ in diameter and the walls are up to 6.5μ in thickness. The walls exhibit simple, oblique, elliptic pits, and sometimes, semibordered pits. The ends are tapering, sometimes undulate or slightly curved, occasionally with an irregular projection near the end, and rarely bifurcate (see Fig. 9). Several crystal fibers are present adhering to some of the wood fibers.

The vascular rays are 1 to 4 cells in width and 2 to 20, rarely up to 27, cells in depth. The cells are rectangular in shape, and they contain starch.

The young roots closely resemble the older roots in general structure, except that the sclerenchyma cells do not form a continuous band in the phloem region. Instead, the stone cells occur in isolated groups of 2 to 33 cells. In slightly older roots, about 20 mm. in diameter, these groups occur in tangentially arranged tiers. The cells in the young roots are less lignified than those in the older roots.

Description of the Powdered Root

The powdered root is yellowish-brown in color and has a slight, indistinct odor. It has a very bitter taste.

Microscopically, the powder shows numerous starch grains, which are simple or 2- to 3-compound, rarely 4-compound (see Fig.

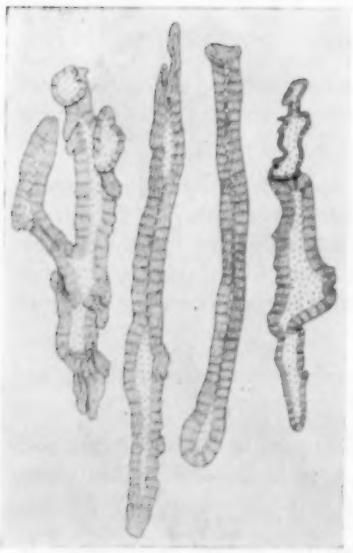


FIGURE 6. Elongated stone cells found in the bark of the root of *Rauwolfia vomitoria* Afz. × 160.

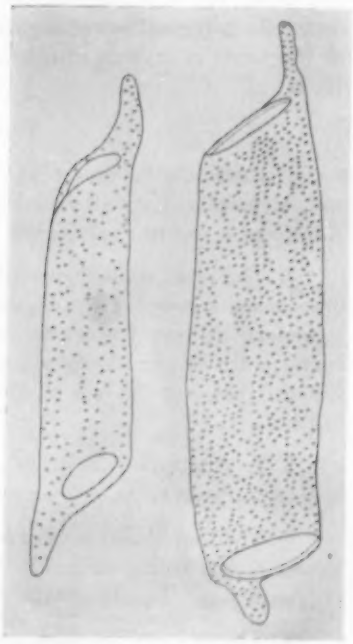


FIGURE 7. Vessel elements found in the root of *Rauwolfia vomitoria* Afz. × 190.

10, A). The individual unaltered grains are up to 26μ in diameter, and the altered grains, generally up to 29μ, sometimes up to 36μ. The grains are spherical, subspherical, pyriform, angular-convex, plano-convex, ovate or subreniform in shape. The hilum is distinct, centric or eccentric, spherical, Y-shaped, stellate, irregularly cleft, or shaped like the wings of a bird in flight. The lamellae are indistinct. The grains show distinct polarization crosses and a play of colors under the selenite plate.

The following are present in the powder: fragments of starch-containing wood parenchyma cells with beaded walls and bordered pits; fragments of fibers, often in groups, characterized by oblique, slit-like pits, sometimes with crossing vascular ray cells; thin-walled parenchyma cells containing starch; fragments of vessel elements and tracheids with transverse, elliptic, simple or bordered pits; characteristic stone cells with very distinct pore canals and simple, round pits; cork cells, polygonal or rectangular in outline; and monoclinic crystals or fragments of crystals of calcium oxalate up to 47μ long (see Fig. 10, B).

Summary

1. *Rauwolfia vomitoria* Afz. has been used as a drug in Africa and, at present, the root is being used in the United States and in Europe as a source of reserpine.

2. The plant is distinguished by terete or obtusely quadrangular branchlets; whorled, glabrous, petiolate leaves with 7 to 21 pairs of secondary nerves; flowers in terminal umbels of finely pubescent cymes; each flower having a corolla up to 8 mm. long and a style which is hairy at the base; and fruiting carpels occurring singly or in pairs.

3. A description is given of the physical characteristics and histology of the roots.

4. The root of *Rauwolfia vomitoria* possesses stratified cork consisting of alternating tangential bands of small, non-lignified walled cells and large, lignified walled cells.

5. The phloem in older portions of the root is traversed by an almost continuous circular band of sclerenchyma elements, interrupted only by phloem rays.

6. The sclerenchyma band in the phloem consists of thick-walled, isodiametric or elongated, branched or unbranched stone cells which measure up to 440μ in length.

7. The wood is made up of numerous wood wedges separated by vascular rays, 1 to 4 cells in width.

8. The wood wedges consist of vessels, tracheids, wood parenchyma cells, wood fibers, and shorter rays.

9. The vessels are arranged in interrupted radial rows, singly or in groups of 2 or 3 within the wood wedges.

10. The vessel elements which measure up to 908μ in length and up to 173μ in diameter, show simple or bordered pits and lateral or terminal perforations.

FIGURE 8. Vessel elements found in the root of *Rauwolfia vomitoria* Afz. × 160.

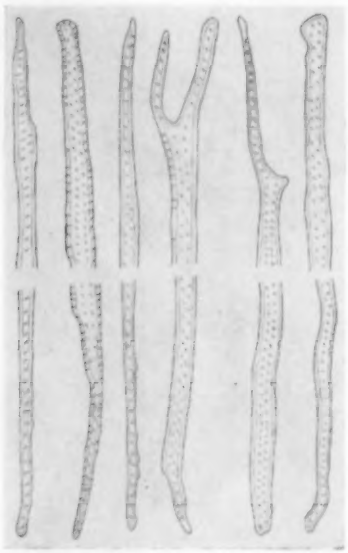


FIGURE 9. Wood fibers. Different types of fiber tips found in the wood region of the root of *Rauwolfia vomitoria* Afz. × 160.

11. The tracheids with tapered ends are pitted similarly to the vessel elements and they measure up to about 342μ in length.

12. The wood fibers, which exhibit simple and semibordered pits, are up to 2400μ long, and are arranged in radial rows.

13. The young roots closely resemble the older roots in general structure except that the cells are less lignified and that there are fewer stone cells in the phloem region.

14. The starch grains are simple or 2- to 4-compound and the individual grains measure up to 36μ in diameter.

15. The monoclinic prisms of calcium oxalate in the root are up to 47μ in length.

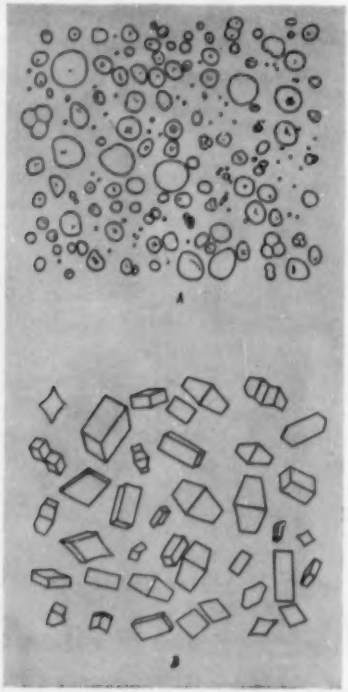


FIGURE 10. Root of *Rauwolfia vomitorai* Afz. A, starch grains; B, prismatic crystals of calcium oxalate. × 190.

Acknowledgment

The authors gratefully acknowledge the generous supply of specimens of roots and overground parts of plants from the Riker Laboratories and the S. B. Penick Co.

BIBLIOGRAPHY

(1) Afzelius, Adam, *Stirpium in Guinea Medicinalium Species Novae*, Zeipel et Palmblad, Upsala, 1818, fasc. 1, pp. 2, 3.

(2) Githens, Thomas S., *Drug Plants of Africa.* African Handbooks: 8, Univ. of Pennsylvania Press, The University Museum, Philadelphia, 1949, pp. 34, 102.

(3) Ramond-Hamet, *Bull. acad. med., 122:*30-38 (1939).

(4) Paris, R., Sur une Apocynacée africaine: le *Rauwolfia vomitoria* Afz., *Ann. pharm. franc. 1:*138-142 (1943).

(5) Schittler, E., Schwartz, R., and Bader, *F. Helv. Chim. Acta 35:*271-276 (1952).

(6) Poisson, J., LeHir, A., Goutarel, R. and Janot, M. M., *Compt. rend. acad. sci., 238:*1607-1609 (1954).

(7) Goutarel, R., LeHir, A., Poisson, J., and Janot, M. M., *Bull. soc. chim. France 11/22:* 1481-82 (1954).

(8) Youngken, H. W., *Pharmaceutical Botany*, 7th ed., The Blakiston Co., Philadelphia, 1951, p. 657.

SELECTED ABSTRACTS

The Use of Gamma Globulin in Measles. Bettag, O. L., Plotke, F., and Sterling, H. M. *Pub. Health Rep. 70*:353 (1955). The effectiveness of gamma globulin in preventing or modifying measles was studied in an orthopedic residence school with 92 disabled children. Gamma globulin was administered on the fourth day of probable exposure following the appearance of the rash in the first child.

A dose of 0.1 ml. of gamma globulin per pound body weight was given to 10 children whose general condition made it seem wise to attempt to prevent the disease. A modifying dose of 0.02 ml. per pound body weight was given to 24 children who had no history of measles. The remaining 58 children were given no gamma globulin since they had a history of measles.

The disease developed in 4 of the children who were given preventive doses of gamma globulin, 2 had German measles and 2 had both. Of the 24 children given a modifying dosage, 19 developed measles, of whom 8 also developed German measles later. Four of the 19 had severe cases and 4 others had complications. Among the 58 students who had previous histories of measles, 20 developed measles, 4 German measles, and 3 had both. Three had some type of complications.

The authors, therefore, concluded that gamma globulin was not effective in the majority of cases in preventing or modifying measles. A previous history of measles was also of no value in deciding who should have received gamma globulin.

Notes on the Sterility Testing of Barbiturates. Booth, T. G. *J. Pharm. and Pharmacol. 7*:268 (1955). The optimal pH for the growth of the majority of bacteria is slightly higher than 7.0. Since solutions of the sodium salts of the barbiturates are quite alkaline, the author decided to test the growth of four test bacteria at various alkaline pH values and also in the presence of various concentrations of sodium salts of barbiturates.

The four test organisms employed were; *Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus subtilis,* and *Escherichia coli.* The sodium salts of barbital, phenobarbital, hexobarbital, and thiopental were used in the study.

Using sterile media in which the pH had been adjusted with N sodium hydroxide solution, the author found that with heavy inocula all four of the organisms would grow up to a pH of about 10.5. As the number of organisms per ml. of media was reduced, the pH at which growth was obtained was also lower. With very low inocula of *E. coli,* growth was not obtained above a pH of about 9.0.

The pH of various concentrations of the barbiturates was obtained. The following pH values were obtained for a 2 per cent concentration of each of the barbiturate salts: barbital sodium 9.62, phenobarbital sodium 9.04, hexobarbital sodium 9.88, and thiopental sodium 9.7. For a 0.2 per cent concentration the pH values were 8.78, 8.4, 8.99, and 8.90, respectively. Bacteriostatic concentrations of the barbiturates in the broth varied with the test organisms, as would be expected. *Staph. aureus* was the most resistant, the bacteriostatic concentrations of the barbiturates were: barbital sodium, more than 7.5; phenobarbital sodium, more than 5.0; hexobarbital sodium, 2.0 to 2.5; and thiopental sodium, 2.0.

From these results the author concluded that in any test for sterility on solutions of these barbiturates the volume of broth employed should be such that the concentration of the barbiturate should not exceed 0.2 per cent. This will avoid a high pH which might prevent the growth of the small number of bacteria most likely to be present. With both hexobarbital sodium and thiopental sodium, increasing concentrations cause precipitation of crystals of the bases. This interferes with observation of turbidity caused by the growth of bacteria. With hexobarbital sodium this difficulty could be overcome by the low concentration of 0.2 per cent in the broth. With thiopental sodium, it was found that after a growth period sufficient sodium hydroxide could be added to just dissolve the thiopental and the bacterial turbidity then read without interference.

The Administration of Salk Poliomyelitis Vaccine to Allergic Patients. Siegel, Sheppard. *Am. J. Pub. Health 45:*791 (1955). The fact that Salk Poliomyelitis Vaccine contains residues of monkey kidney tissue and because 200 units of penicillin is added

to each ml. of culture medium, the question has been raised as to whether or not the vaccine is safe to administer to patients allergic to animal proteins and to penicillin.

The authors performed intracutaneous and subcutaneous tests of the undiluted vaccine on 16 adult patients with allergic rhinitis and asthma due to multiple pollen, inhalant and food sensitivity and with strongly positive skin test reactions to animal danders. Only 2 of these patients showed a slight reaction to the subcutaneous injection and none of those given the subcutaneous injection showed any local or systemic reaction.

In a patient with persistent penicillin sensitivity, intracutaneous tests showed slight initial erythema which completely subsided within 48 hours. A concentration of 10 units per ml. of crystalline penicillin G elicited a reaction of bright erythema which was almost unchanged after 48 hours.

Among 63 consecutive control adult subjects, intracutaneous tests with poliomyelitis vaccine showed negative initial reactions. Of 58 adults given subcutaneous injections negative initial reactions were obtained in 39. Within 48 hours all reactions had almost completely subsided.

The author, therefore, concluded that these results substantiate the results already obtained in thousands of routine injections, that Salk Poliomyelitis Vaccine should offer no hazard to persons allergic to animal proteins or to penicillin.

An Evaluation of Hydrocortisone Ointment in Pruritic Dermatoses. Russell, B., Pegum, J. S., Thorne, N. A., and Grange, R. V. *The Lancet I:*1038 (1955). Hydrocortisone in a polyethylene glycol base in a concentration of 1 or 2.5 per cent was applied alternately with the base alone, each for one week, in a series of 132 patients with various pruritic conditions. The patient was unaware that an alternation between base and a therapeutic ointment was employed and the clinician did not know which was used first.

An analysis of the results, largely based upon the subjective record of the patients, indicated that hydrocortisone ointment was highly effective in lichen simplex, discoid eczema, otitis externa, and anogenital pruritus. Improvement was less evident in infantile eczema and in idiopathic eczematous dermatitis of the hands. In Besnier's

prurigo local improvement was sometimes obtained but the general results were poor. In pruritic anogenital psoriasis the results were equivocal with practically as good a result obtained with the base alone.

No evidence of local or systemic ill effects were observed following the use of hydrocortisone ointment. One patient did show sensitivity to the base but later improved when a hydrous type base was employed.

Progress was maintained with more prolonged treatment after the two-week study period in cases of lichen simplex, discoid eczema, anogenital pruritus and otitis externa. Sedative drugs often had to be used to control the effects of outside influences.

The Chemical Reversal of Ultraviolet Effects on Certain Bacteria. Ellison, S. A., Erlanger, B. F., and Allen, P., *J. Bact. 69*:536 (1955). It has been established that the effects of ultraviolet radiations can be reversed in some instances by exposure to strong illumination in the visible or near ultraviolet range. It was postulated that there is similarity between this photoreactivation and photosynthesis in the initial step. It has also been suggested that 6,8-dithiooctanoic acid, widely distributed in bacteria, might be the photodynamic substance concerned in photosynthesis. In some instances, it has been found that high concentrations of acetate can substitute for 6,8-dithiooctanoic acid.

Therefore, sodium acetate in varying concentrations was added to nutrient agar and the ultraviolet irradiated organisms were plated in this medium. The organisms employed were *Escherichia coli* strain B, *E. coli* strain B/15-17 (an ultraviolet resistant mutant), and *Corynebacterium bovis*.

Both the lethal and the mutagenic effects of the ultraviolet radiation on *E. coli* strain B and *C. bovis* were reversed by the sodium acetate in the medium. The degree of reactivation was directly proportional to the concentration of sodium acetate. A maximum was obtained at a concentration of about 25 mg. of sodium acetate per ml. of medium. Although *E. coli* strain B/15-17 was photo reactivated it was not reactivated by the sodium acetate. It would appear, therefore, that the two reactivation mechanisms are basically dissimilar.

The Treatment of Infectious Hepatitis With Tetracycline. Wodraska, T. W. *Antibiot. Med. 1:327* (1955). An epidemic of the viral disease, infectious hepatitis, occurred in a mental institution. The first cases occurred in the month of May with the last few cases occurring the early part of the following December. Several weeks sometimes occurred between the appearance of a new group of cases and the previous group. All suspected and proved cases were placed in strict isolation.

In buildings where cases of infectious hepatitis occurred, a massive prophylaxis was done with gamma globulin. The dosage was kept at 0.02 and 0.1 ml. per pound of body weight, the latter for the older patients. Nearly 2000 persons were given prophylactic treatment with gamma globulin. These included both patients and employees. It was found that when all patients and personnel in a particular building were immunized at the same time the epidemic was brought under control. However, when the immunization was given ward by ward with intervals of several weeks, the epidemic was not controlled. Thus, it was concluded that if gamma globulin is given soon enough and on a wide enough scale it appears to be an effective prophylactic.

In all, 60 patients contracted the disease. Forty-five of these patients were given 1.0 to 1.5 Gm. of tetracycline a day, orally, in 4 divided doses over a period of 10 to 12 days. The remaining 15 patients were given only the usual bed rest and diet therapy. Tetracycline was effective in 80 per cent of the treated cases. In 3 of the 9 patients in whom treatment was not effective there was definite liver damage. In response to tetracycline therapy, there was a noticeable clinical improvement within a few days and the duration of illness was shortened from the usual 5 to 8 weeks to 1 to 2 weeks with tetracycline therapy. Careful laboratory studies were performed in all of the patients.

Local Management of Dermatoses With Hydrocortisone. Robinson, H. M., Jr., Robinson, R. C. V., and Strahan, J. F. *Med. Times 83:227* (1955). A large group of patients, 1655, with various dermatoses were treated with hydrocortisone alcohol, hydrocortisone acetate, and combinations of hydrocortisone with various antibiotics.

These substances were incorporated into a variety of vehicles for topical application, including lotion bases, greaseless bases, and oily bases. Twenty-three different preparations were employed with the steroid present in concentrations of 0.5, 1.0 and 2.5 per cent.

As a result of this study it was found that temporary remission of symptoms of atopic dermatitis, neurodermatitis, allergic contact dermatitis, stasis dermatitis, pruritus ani, and pruritus vulvae could be obtained. In most instances continued applications were necessary to maintain the dramatic effect, but it was often possible to reduce the concentration and the frequency of application. Although the concentration of 0.5 per cent of the steroid in an oily base was effective therapy in about 60 per cent of the patients treated, its greatest usefulness is probably in maintenance therapy after treatment has been initiated with the 1.0 or 2.5 per cent concentration. No appreciable difference was found between the local action of hydrocortisone and hydrocortisone acetate. Frequently, it was found that systemic therapy with hydrocortisone could be discontinued and topical therapy used in its place.

In this large series of cases it was found to be evident that the oily base preparations are the most efficacious, are less irritating, and require a smaller quantity to cover a larger area than a comparable amount of a greaseless cream base. Local irritations were observed in 81 of the patients, but in each case the irritation was found to be due to the vehicle and not to the medicinal substance.

The addition of tetracycline, oxytetracycline, neomycin, bacitracin and erythromycin to these preparations provided the additional advantage of eradicating secondary infections. There was no interference with the action of either the steroid or the antibiotic.

Local Anesthetic Solutions in Dentistry. Tainter, M. L., Wessinger, G. D., and Lee, J. W. *J. Am. Dent. Assoc. 51:*19 (1955). Six local anesthetic solutions were used and evaluated by approximately 300 dentists from all over the nation in 13,908 cases. The solutions employed were so-called fortified solutions in which a more potent compound was added to the usual 2 per cent procaine hydrochloride in solution. In this way the virtues of procaine, particularly

its freedom from systemic toxicity and local irritation, were maintained while the potency was increased by the stronger compound without significant prolongation of action.

The potentiating agents employed were either tetracaine hydrochloride 0.15 per cent or a new local anesthetic, propoxycaine hydrochloride 0.4 per cent. The vasoconstrictor was either levarterenol 1:30,000 or Nordefrin 1:10,000. The reference solutions were procaine hydrochloride 2 per cent with either 1:50,000 or 1:60,000 epinephrine.

The solution containing procaine hydrochloride, propoxycaine hydrochloride and levarterenol (RNL) produced the highest incidence of completely satisfactory anesthesia, 90.7 per cent. The percentage of completely satisfactory anesthesia with the propoxycaine hydrochloride, procaine hydrochloride, and Nordefrin (RNC) was 88.1, with the procaine hydrochloride, tetracaine hydrochloride, and levarterenol (NPL) was 88.3, with procaine hydrochloride, tetracaine hydrochloride, and Nordefrin (NPC) was 83.1, and with the procaine hydrochloride and epinephrine solutions (NE) was 84.5. The onset of anesthesia (80 seconds) was shortest with the RNC solution. The total duration of anesthesia was shortest with the NE solution and longest with the NPL solution. The amount of bleeding was essentially the same with each of the solutions. The solution with the highest proportion (96 per cent) of complete freedom from systemic reactions was the RNL combination. None of the solutions induced significant post-operative tissue reactions.

The authors, therefore, concluded that these fortified solutions, particularly those containing propoxycaine hydrochloride, produced a higher reliability of anesthesia without an increased incidence of untoward side effects.

BOOK REVIEW

The National Formulary, Tenth Edition. Compiled and edited by the Committee on National Formulary. Published by the American Pharmaceutical Association, Washington, D. C. Distributed by J. B. Lippincott Company, Philadelphia, Pa. 15.5 × 23.5 cm. xliii + 867 pp. Price $9.00.

The recently published Tenth Edition of the National Formulary represents one of the most extensive revisions of its entire history extending over a period of 67 years. This edition is the result of work of the Committee on National Formulary, supplemented by advisory committees, extending over a 5-year period.

In the course of the revision, 474 of the 717 N. F. IX monographs were continued in N. F. X. The deletion of the unprecedented number of 243 items is accounted for, in part, by the rapidity with which drugs become obsolete, and in part by the fact that a substantial number of N. F. IX monographs was admitted to U. S. P. XV on the basis of their therapeutic or pharmaceutical essentiality. Of the 733 monographs included in N. F. X, 128 cover other extensively used drugs of therapeutic importance for which official standards would not otherwise be provided. In this group are included such drugs as the amphetamine phosphates, the choline salts, dihydrocodeinone bitartrate, dihydroxyaluminum aminoacetate, glycobiarsol, inositol, mephenesin, mephobarbital, nitrofurazone, methaphenilene hydrochloride, pheniramine maleate, promethazine hydrochloride, protamine sulfate injection, quinidine gluconate, dosage forms combining two or more sulfonamides, five monographs covering the different types of tocopherol representing vitamin E activity, and vinbarbital. In most instances dosage forms have been provided for any basic drug admitted to N. F. X.

During the revision of the U. S. P. leading to the publication of the fifteenth revision, 160 drugs and preparations were deleted. Many of these drugs will doubtless continue to be used for many years, and specifications for 131 in this group were admitted to N. F. X. In this category are included such drugs and dosage forms as aspirin capsules, barbital, boric acid ointment, codeine sulfate,

digitalis tincture, ephedrine hydrochloride, estradiol, gentian, hydriodic acid syrup, magnesium citrate solution, ox bile extract, pancreatin, several sulfonamides, and combinations of theobromine with salicylates and acetates.

Despite the inherent limitations on scope because of the book's legal status, a section on "General Information" has been added as a new and useful feature to the new edition of the National Formulary. In this new section will be found general information relating to balances, weights, and measuring devices; chiropody-podiatry drugs and preparations; clinical laboratory reagents and staining solutions; certified coal-tar colors; the International Pharmacopoeia; optical crystallographic characteristics of drugs; and a chapter on sterilization.

The chapter on balances, weights, and measuring devices describes the prescription balance, defines such terms as capacity, weighbeam, tare bar, balance indicator, rest point, sensibility reciprocal, and sensitivity. Specifications for Class A and Class B prescription balances, and methods of testing the accuracy of these balances are also included. Specifications for preferred types of weights and measuring devices are outlined, and a chart is provided compliance with the specifications outlined.

The N. F. chapter on clinical laboratory reagents has been considerably condensed to furnish only a limited number of formulas for standard preparations supplied by pharmacists for use in physicians' offices. The new chapter, while limited in scope, supplies most formulas required by the pharmacist in furnishing the more commonly used clinical laboratory reagents and staining solutions.

In N. F. X a chapter designed to furnish certain basic information relating to dyes used for coloring pharmaceutical preparations has been added. This basic information includes discussions on restrictions on the use of dyes, the choice of a coal-tar color, and the application of coal-tar colors to liquids and to powders. Several useful tables covering the physical properties of selected coal-tar colors have been added. Of particular importance are tables listing 24 coal-tar colors from which dyes suitable for coloring most pharmaceutical preparations can usually be chosen.

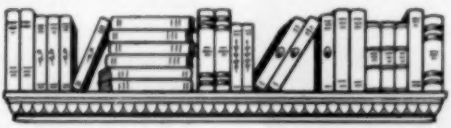
The table of optical crystallographic constants of N. F. crystalline substances, a feature of previous editions, has been completely revised and expanded to include optical data for nearly all N. F.

crystalline substances. A discussion of methods, reagents, and procedures for the determination of refractive indices, extinction angles, elongation, and optical and axial angles has been added to supplement the revised table.

A chapter on sterilization furnishes general information on this important subject and may serve to emphasize the general types of manufacturing control that must be exercised in the preparation of parenteral solutions meeting the official sterility requirements. Another useful feature new to the National Formulary is a table comparing titles and certain specifications for International Pharmacopoeia drugs covered by the specifications in the National Formulary.

The style and format of the Tenth Edition of the National Formulary are essentially the same as in N. F. IX. A new and useful feature added to each monograph gives the main pharmacological or pharmaceutical category of the drug or preparation covered. The usefulness of the book has been enhanced by a streamlining of the general index and the addition of indices preceding the General Notices, the General Tests, Processes, and Apparatus, and the new section on General Information. The new edition is attractively bound in a durable blue Fabrikoid, and the printing is of the same quality as in previous editions of the National Formulary.

The publication of the new edition will be of particular interest to practicing pharmacists and to manufacturers of pharmaceuticals and basic medicinal chemicals and like its predecessors, constitutes a distinguished service of the American Pharmaceutical Association to the development of effective legal standards for drugs. It also serves as a useful reference book on the characteristics of a large number of widely used drugs and therapeutic preparations.



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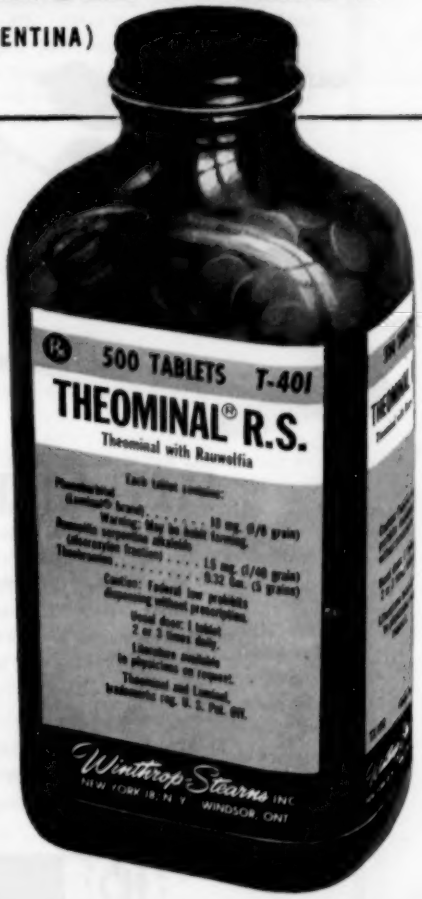

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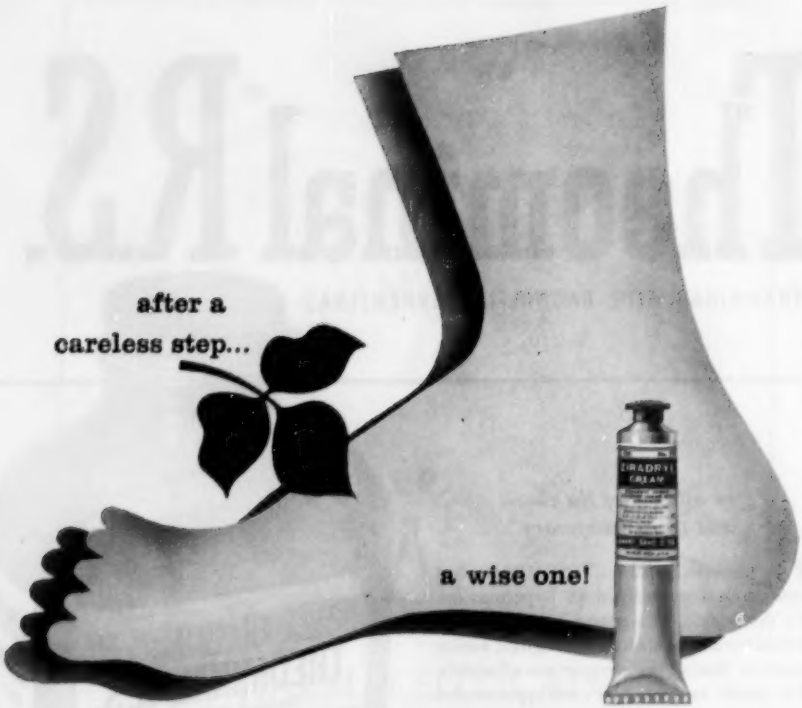

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